In The Specification

Please delete the paragraph at page 9, spanning lines 8 – 23, and insert the following replacement paragraph:

In further embodiments, the methods may include contacting an appropriate cell type expressing a temperature sensitive oncogene, *e.g.*, simian virus 40 large tumor antigen (tsSV40Tag), *in vitro*, *ex vivo*, or *in vivo* with an antigen to produce an antibody. In certain aspects, antibody producing cells, preferably splenocytes, are isolated and immortalized from a mouse expressing tsSV40Tag. In one such mouse, the ~~ImmortoMouse~~IMMORTOMOUSE®, a H-2K^b-tsA58 transgenic mouse, expression of the nucleic acid encoding a tsSV40Tag is under the control of the major histocompatibility promoter (Jat *et al.*, 1991, incorporated herein by reference in its entirety). Cells derived from an ~~ImmortoMouse~~IMMORTOMOUSE® remain immortal if cultured at 33°C (Jat *et al.*, 1991). Various methods and compositions comprising transgenic mice and cells derived from transgenic mice expressing tsSV40Tag are described in the patent literature, for examples see U.S. Patents 6,399,384; 5,866,759; 5,688,692; and 5,270,191, each of which is incorporated herein in its entirety. In other aspects, antibody producing or antigen presenting cells may be isolated and cultured from various tissues of a tsSV40Tag expressing animal including, but not limited to bone marrow, thymus, brain, or reproductive tissue. In still other aspects, stem cells may be isolated and cultured from such tissue samples.

Please delete the paragraph at page 9, spanning lines 24 – 27, and insert the following replacement paragraph:

In still further embodiments, harvested cells (*e.g.*, from an ~~ImmortoMouse~~IMMORTOMOUSE®) may be contacted with one or more antigen(s) followed by evaluation of production of antibody against the antigen, including assessment of the specificity of antigen binding. Various sub-populations of the cells may be made or cloned and stored for future use.

Please delete the paragraph at page 11, lines 8 – 20, and insert the following replacement paragraph:

An animal expressing a transforming protein is immunized (*e.g.*, H-2Kb-tsA58 ~~ImmortoMouse~~IMMORTOMOUSE®) or cells expressing a transforming protein are exposed to an antigen (*e.g.*, filamentous fd-tet phage (Zacher *et al.*, 1980)) in order to induce production of an antibody that binds an antigen of interest. The immunization or contact may be repeated one or more times over various periods of time, for example immunization or antigen exposure may be once every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or more days or weeks. In certain aspects immunization or antigen exposure may be every other day or week, or every third, fourth, fifth or more day or week. Immunization or antigen exposure may be carried out over 2, 3, 4, 5, 6 7, 8, 9, 10, 11, 12, 13, 14, 15, or more weeks and even months, preferably for about 12 weeks. An antigen preparation is administered by one or more routes, including intravenous (i.v.), intraperitoneal (i.p.), intradermal, subcutaneous (s.c.) or various combinations thereof. Animals may be bled after each boost and ELISA used to monitor anti-antigen antibody titers in the serum.

Please delete the paragraph at page 14, spanning lines 11 – 15, and insert the following replacement paragraph:

In certain embodiments of the present invention, immortalized splenocytes derived from transgenic mice harboring a mutant temperature-sensitive (ts) simian virus 40 (SV40) large tumor antigen (Tag) under the control of a mouse major histocompatibility promoter (named H-$2K^b$-tsA58 transgenic mouse; ~~ImmortoMouse~~IMMORTOMOUSE®) are immortal and alleviate the need for hybridoma production.

Please delete the paragraph at page 15, spanning lines 4 – 13, and insert the following replacement paragraph:

To direct expression to a broad range of tissues a mouse major histocompatibility complex H-2Kb promoter that is both widely active and can be induced by interferons was used. The tsSV40TAg mRNA was expressed in tissues of all animals harboring the hybrid construct.

Development of all tissues was macroscopically normal. One strain of H-2Kb-tsA58 mice has been bred through several generations to homozygosity and transmits a functional copy of the transgene. These mice are termed "ImmortoMice." The ~~ImmortoMouse~~IMMORTOMOUSE® is commercially available from Charles River Labs, Wilmington, MA. Many different types of conditionally immortal cell lines have been derived from ~~ImmortoMouse~~IMMORTOMOUSE® but, this well established mouse model has not been exploited for the generation of monoclonal antibody-producing cells.

Please delete the paragraph at page 15, spanning lines 14 – 22, and insert the following replacement paragraph:

~~ImmortoMouse~~IMMORTOMOUSE® was developed for its ability to generate expanded populations of individual cell types able to undergo normal differentiation *in vitro* and *in vivo* for use in the investigation of the cellular mechanisms of differentiation and for cell transplantation studies related to tissue repair. The H-2Kb-tsA58 mouse allows the direct derivation of conditionally immortal cell lines from a variety of tissues by the growth of isolated cells under appropriate conditions. In these mice the tsSV40Tag is controlled by the interferon-inducible Class I antigen promoter. Cells can be grown for extended periods *in vitro* by growing them at 33°C in the presence or absence of interferon, while still retaining the capacity to undergo normal differentiation *in vivo* and *in vitro*.

Please delete the paragraph at page 15, spanning lines 24 – 28, and insert the following replacement paragraph:

In one embodiment of the invention, transgenic mice comprising a conditionally functional transforming oncogene, *e.g.*, an ~~ImmortoMouse~~IMMORTOMOUSE®, may be crossed with transgenic mice harboring genes from other species encoding various genetic components for antibody production (as detailed below) to generate cell lines producing antibodies of the other species, such as human antibodies.

Please delete the paragraph at page 16, spanning lines 1 – 18, and insert the following replacement paragraph:

The ability to produce a diverse repertoire of fully human monoclonal antibodies has applications in human therapy. One of the most promising approaches to the production of therapeutic human polyclonal or monoclonal antibodies is the creation of a mouse strain engineered to produce a large repertoire of human antibodies in the absence of mouse or other non-human antibodies (*e.g.*, ~~XenoMouse~~XENOMOUSE®). Recently, mice have been generated by introducing segments of human immunoglobulin loci into the germline of mice deficient in mouse antibody production as a result of gene targeting. These mice produce significant levels of fully human antibodies with a diverse adult-like repertoire and, upon immunization with antigens, generate antigen-specific human antibodies. The ~~XenoMouse~~XENOMOUSE® is equipped with approximately 80% of the human heavy chain antibody genes and a significant amount of the human light chain genes. The complex assembly of these genes together with their semi-random pairing allows the mouse to recognize a diverse repertoire of antigen structures. In addition, the mouse is capable of processing extremely high affinity, completely human antibodies. There are multiple strains of ~~XenoMouse~~XENOMOUSE® animals available. Each strain is capable of producing a different class of antibody for various applications. Such strains of mice may provide the optimal source for producing human antibodies with high affinity and specificity against a broad spectrum of antigens, including human antigens.

Please delete the paragraph at page 16, spanning lines 19 – 28, and insert the following replacement paragraph:

The ~~XenoMouse~~XENOMOUSE® generates antibodies with fully human protein sequences using genetically engineered strains of mice in which mouse antibody gene expression is suppressed and functionally replaced with human antibody gene expression, while leaving intact the rest of the mouse immune system. By introducing human antibody genes into the mouse genome, transgenic mice with such traits can be bred indefinitely. Importantly, these transgenic mice are capable of generating human antibodies to human antigens because the only human products expressed in the mice (and therefore recognized as "self") are the antibodies

themselves. All the other machinery is mouse machinery, thus any other human tissue or protein is recognized as foreign by the mouse and an immune response will be mounted.

Please delete the paragraph at page 16, spanning lines 29 – 31 and page 17 lines 1-8, and insert the following replacement paragraph:

Abnormal synthesis of some human proteins, for example cytokines hormones and growth factors or their receptors, contribute to various human diseases. Regulating these proteins by neutralization or total elimination using human antibodies may be used to treat or completely eliminate the disease. The ability of these transgenic mice to generate cells that may be used in production of human antibodies against human antigens could offer an advantage in the treatment, diagnosis, or cure of various disease states. One challenge has been to produce enough of a human antibody against a given antigen in a stable cell line. This problem may be solved by embodiments of this invention. In one embodiment, a cross-bred mouse population (*e.g.*, ~~ImmortoMouse®/Xenomouse®~~IMMORTOMOUSE®/XENOMOUSE® cross) may produce immortalized splenocytes capable of producing antibodies against any human antigen without the need to produce hybridomas.

Please delete the paragraph at page 17, spanning lines 9 – 21, and insert the following replacement paragraph:

The ~~XenoMouse~~XENOMOUSE®, or animals with similar genetic modifications, generate antibodies with 100% human protein sequences that differ from chimeric and other humanization technologies. Other advantages of using these mice are that the antibodies produced using ~~XenoMouse~~XENOMOUSE® technology may be expected to offer a better safety profile and to be eliminated less quickly from the human body, reducing the frequency of dosing.

~~XenoMouse~~XENOMOUSE® technology uses the natural *in vivo* affinity maturation process to generate antibody product candidates usually in two to four months. These antibody product candidates may have affinities as much as a hundred to a thousand times higher than those seen in phage display. In contrast to antibodies generated using humanization and phage display technology there is no need for any subsequent engineering, a process that at times has

proven to be challenging and time consuming. Therefore, an antibody's structure may remain intact from the initial antibody selected to the final commercial antibody.

Please delete the paragraph at page 23, spanning lines 4 – 11, and insert the following replacement paragraph:

Once a candidate target is identified as the receptor of a targeting peptide, it can be isolated, purified and cloned by using standard biochemical methods (Pasqualini, 1999; Rajotte and Ruoslahti, 1999). These purified proteins may then be used as an antigen for immunization or exposure of a cell population such as splenocytes from an ~~ImmortoMouse~~IMMORTOMOUSE®, an ~~ImmortoMouse~~IMMORTOMOUSE® cross producing humanized cell populations or other conditionally immortalizable cell lines, such as monoclonal antibody producing splenocytes. Then these antibody-producing cells may be used to generate specific antibody populations against the targeted receptor or antigen.

Please delete the paragraph at page 37, spanning lines 14 – 27, and insert the following replacement paragraph:

Another use for immortalized cells may be in replacing the stem cell population of a diseased subject. In one example, one might irradiate the marrow of an animal such as a mouse, and replace it with the marrow or any source of stem cells from an immortalized animal such as an ~~ImmortoMouse~~IMMORTOMOUSE®. To analyze any results, the normal animal may be sacrificed to identify any stem cells that may be immortal, which came from the ~~ImmortoMouse~~IMMORTOMOUSE®. This will allow the identification of specific organ homing stem cells. Also, crossing an ~~ImmortoMouse~~IMMORTOMOUSE® with a Rosa mouse (expressing Lac Z in all cells) will also help in not only growing but tagging the cells coming from the ~~ImmortoMouse~~IMMORTOMOUSE® to allow tracking in the recipient.

Brain stem cells from the ~~ImmortoMouse~~IMMORTOMOUSE® have been isolated and characterized. The smallest cells growing by the round cells in FIG. 5, lowest right panel, appear to be spleen stem cells. Thus, isolation of immortalized stem cells and introduction of this population may be used in the future to improve the chances of survival of compromised subjects such as cancer patients.